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BY J. MORRIS SLEMONS, M.D.

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THE NUTRITION OF THE FETUS*

PREGNANCY is essentially a problem in nutrition, and at this time the dominant metabolic forces are those which favor growth. The mother's gradual but consistent gain in weight amounts finally to about 30 pounds; exceptionally, it is as little as 10 to 15 pounds, and at the other extreme as much as 40 to 50 pounds. With individuals inclined to be stout the increase is greater; and it is relatively greater in later pregnancies than in the first. During the early months of gestation the weight generally remains stationary or suffers a slight loss; even in those instances in which the weight begins to increase shortly after conception, the gain is less marked in the early months than later. For the last three months the average monthly gain has been found to be between 3.5 and 5.5 pounds.

The mother's increase in weight is at-

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tributable in part to the fetus, the placenta, the amniotic fluid, the uterus, and the breasts; but to some extent all the maternal tissues respond to the stimulus toward growth. Probably the relative importance of this last factor is too easily overlooked, for, naturally, the special development of the ovum first seizes upon and is likely to monopolize the attention. On the other hand, the extent of the participation of the mother's body in the growth of the gestation period may be shown by a simple arithmetical calculation. Thus, if the weight of the product of conception at full term together with that of the parturient uterus is deducted from the mother's total gain in weight, it appears that only about half of her increase is accounted for. Obviously, the remainder must be ascribed to her body tissues in general. This fact suggests the correct answer to a question which physiologists have often submitted to experiment, namely, "Does the material provided for the growth of the ovum come from the mother's tissues or from her food?"

I

At first it was believed that, for the mother, pregnancy constituted a period of sacrifice and that fetal growth occurred at the expense of her tissues. Exceptionally, if the mother's food is inadequate, this may be true. It is conceivable, too, that small amounts of various materials derived from the mother's tissues may be contributed regularly to the ovum while its implantation is in progress, but in a quantitative sense the requirements of the very early stages of development are negligible, and the period itself is a brief one, probably no longer than the time required for adjustment between the blastocyst and the uterine circulation.

With data at hand to support it, the current view holds that pregnancy represents for the mother a period of gain, rather than of sacrifice, and accordingly that her tissues are not deprived of material to supply the new organism. Both animal experiments and observations upon women indicate that the mother's food

furnishes the substances incorporated in the body of the fetus. Thus, in the case of dogs, elaborate analyses of the food on the one hand and of the excreta on the other teach that a notable storage of the foodstuffs is characteristic of pregnancy. Furthermore, if this storage is compared with the amount of material contained in the bodies of the young it appears that the mother's food is sufficient not only to meet her own requirements, but also those of fetal development. Similar studies in which Bar selected rabbits as the subject of experiment led to an identical conclusion. And with regard to women, Wilson concludes from his extensive studies of nitrogenous metabolism during pregnancy that an ordinary diet provides for every fetal requirement and permits storage to begin in the maternal organism at a much earlier period than was generally supposed; perhaps it begins at the very outset of pregnancy.

What are the substances required for fetal nutrition? This question may be answered in two ways. On the one hand, we may infer the needs of the fetus from those of the newborn infant which, of course, is

sustained by its mother's milk, a fluid of familiar composition. Or, on the other hand, upon the fair assumption that the substances found in the fetus represent its requirements for growth we may resort to the analysis of its body. From information of this kind we conclude that there is no great difference between the fetus and the adult so far as the quality of the food they require is concerned: in their life processes both use the same organic and inorganic substances which are always available in the circulating blood of the mother.

The constitutents of the mother's blood include nutrient nitrogenous substances, carbohydrate, fat, oxygen, water, and inorganic salts; together these meet all the requirements for tissue growth and energy production. That they are at the disposal of the fetus, there can be no question, but it is equally certain that none of these materials may pass directly into its circulation. Across the path traversed by these substances on their way from the parent to her offspring lies a complex organ, the placenta, composed partly of a specialized uterine tissue but mainly of elements de-

rived from the luxuriant development of a portion of the fetal membranes—the chorion frondosum. The obstructive action of the placenta was demonstrated by the experiments of John and William Hunter. These investigators proved that the mother's blood never enters the fetus and also that the reverse phenomenon is impossible. More recently, and especially after the invention of the microscope and improvements in histological technique, embryology has gradually accumulated the facts which now make the chapter on the morphology of the placenta both intimate and nearly complete.

The architectural arrangement of this organ which accommodates simultaneously the fetal and maternal circulations, yet holds them apart, is so well known that there is no longer any doubt regarding the path each follows. Venous blood from the fetus enters the placenta by way of the umbilical arteries, which divide again and again to form a multitude of capillaries. Subsequently, these reunite into a single vessel, the umbilical vein, through which the arterialized blood returns to the fetal heart.

Chiefly by the division and subdivision of the fetal vessels in the placenta, an extensive vascular bed is created. The bed is notably enlarged by the arrangement of the smallest of these vessels, which form loops hanging toward the maternal blood. With this, however, the fetal vessels do not come into direct contact, for they are covered with connective tissue and this in turn with embryonic epithelium. Together with their enclosing layers of tissue the capillary loops constitute the chorionic villi. During the early months of pregnancy the epithelial covering of the villi forms two layers but later is reduced to a single layer of about the thickness of endothelium. Thus, the thickness and complexity of the placental partition varies inversely with the nutritional requirements of the new organism, for at first the material requirements of the embryo are infinitesimal. Although they increase gradually, these requirements are insignificant in a quantitative sense until after the 18th to 20th week of pregnancy; and about this time also the simplification of the placental partition takes place. Indeed, it is not unlikely that the anatomical

transition is intended to promote the physiological interchange between the fetal and maternal circulations, thus to secure for the new organism a more rapid rate of growth.

The maternal blood, which supplies the fetus with everything it needs and coincidently removes its excretory products, enters the placenta through the branches of the uterine arteries and departs through the uterine veins. As it passes through this organ, the mother's blood comes into contact with the surface of the villi where the requisite exchange of foodstuffs and waste products takes place. Certain substances pass in one direction while others are passing in the opposite direction; but all traverse the same placental partition which, as we have seen, consists in the latter half of pregnancy of a thin covering of epithelium, a layer of connective tissue and, within this, the delicate wall of the fetal capillary.

How substances pass through the placental partition is a question answered, thus far, only hypothetically. There has been no lack of speculation on the subject. In the main two antagonistic theories have

been developed; one of these, the vitalistic, assumes that the wall of the chorionic villus takes an active part in the placental interchange; the other, the mechanistic, regards this wall as a passive, semi-permeable membrane conforming with the laws of osmosis and diffusion.

1. *The Vitalistic Hypothesis.* That the placenta actually digests the food of the fetus was suggested by William Harvey, who attempted to establish a complete analogy between the chorionic and the intestinal villi. This view gained many adherents after Hofbauer and others demonstrated the presence of enzymes in the placenta, though it was never shown that these lipolytic, diastatic, and proteolytic enzymes are agents in the placental interchange. On the contrary, it is likely that they have to do only with the living processes of the cells which contain them.

2. *The Mechanistic Hypothesis.* In the transmission of a few substances, it has been positively proved that the placental partition plays a passive rôle and behaves as a semi-permeable membrane. Thus, oxygen and carbon dioxide, we are taught by the experiments of Cohnstein and

Zuntz, pass equally well from mother to fetus or in the opposite direction, and always move from the point of higher to that of lower concentration. Probably the laws of diffusion apply to the placental transmission of the anaesthetics, chloroform, ether, and nitrous oxide; though they do not apply to gases, like carbon monoxide, which enter into chemical combination with haemoglobin. Cohnstein and Zuntz found also that sodium chloride passed the placenta by osmosis. The evidence they obtained relative to the transmission of glucose was not conclusive, though it seemed likely that osmosis was the process concerned.

II

One fundamental fact regarding placental transmission was established by the experiments of Gusserow and his associates, namely, provided the placenta is normal, no insoluble substance may pass it. The formed elements of the blood are confined to that circulation in which they originate; consequently, an infant whose mother is suffering from leukaemia, presents a normal blood picture. Moreover, cinnabar, barium sulphate, and other insoluble compounds, when introduced into either the mother or the fetus, are effectually confined within the circulation where they are introduced. On the other hand, a variety of soluble substances when injected into the mother may be detected later in the fetus; and the reverse experiment yields analogous results. From reports of such tests, Kehrer stated in 1907 that of 73 substances examined 43 were found to pass readily through the placenta. Many of the latter substances are poisonous and, indeed, were selected for that

reason, because a toxic action often assists in determining the result of such an experiment. Thus, strychnine, hydrocyanic acid, nicotine, curare, pilocarpine, physostigmine, phloridzine, sodium sulphate, methylene blue, and epinephrine have been demonstrated in the mother after they were injected into the fetus.

With the exception of carbon dioxide, no fetal excretory product has been the subject of serious investigation. The suggestion of Halban and Fleck, that the chorionic villi elaborate an internal secretion which controls fetal excretion, proceeds entirely from theoretical considerations. "At present," we read in "Döderlein's Handbuch der Geburtshülfe (1915)," "it is impossible to say more than that fetal waste products make their way to the placenta and through it reach the maternal organism which subsequently eliminates them."

Since so little is known of the principles involved in the placental interchange, and direct study of the problem by means of animal experimentation is limited by almost insurmountable difficulties, we have turned to clinical observations in the hope

of learning what is the character of the mechanism in question. We secured specimens of maternal and fetal blood simultaneously, just after the infant was born. The fetal blood was obtained from the placental end of the severed cord, the maternal from one of the veins in the forearm.

Current methods of chemical analysis yield accurate results even with small specimens of blood. Therefore, at times, in a given specimen we were able to estimate a number of its ingredients, but more frequently we were restricted to the estimation of one or two. Although this limitation has made progress slow, it has had the effect of increasing the number of cases studied and thus broadened our experience. We have gathered data, thus far, relative to the organic foodstuffs, protein, carbohydrate, and fat; and it will be convenient to discuss them separately, in the order named, considering the waste products of nitrogenous metabolism along with the foodstuffs from which they are derived.

III

PROTEIN, distinguished among the foodstuffs because it contains the chemical element, nitrogen, may not be utilized directly by our tissues. Intestinal digestion breaks down protein into much simpler nitrogenous compounds, the amino acids, which are absorbed into the blood stream and distributed to every part of the body. The amino acids are used both for construction and repair; and, according to the organ which employs them, they are built into one variety of protein or another, probably of a very different character from that of the protein in the diet which originally supplied them.

Now, tissue metabolism, which is the name given the intricate and poorly understood phenomenon just referred to, has another side. As long as life lasts tissue protein is being torn down, or perhaps burned down, with the result that chemical compounds are formed which our bodies are incapable of utilizing; therefore, they are called waste products. These com-

NON-PROTEIN NITROGEN AND UREA NITROGEN

OF THE WHOLE BLOOD

No.	Source	Para	N.P.N. mg. per 100 cc.	Urea-nitrogen mg. per 100 cc.	Remarks
1	Mother Fetus	I	20.2 20.5	9.3 8.9	No anaesthetic.
2	Mother Fetus	I	26.5 27.2	9.8 10.7	Whiffs of chloroform.
3	Mother Fetus	I	21.7 20.0	9.3 8.4	Whiffs of chloroform.
4	Mother Fetus	I	20.0 19.0	9.8 11.7	Deep chloroform.
5	Mother Fetus	II	22.5 22.0	9.8 9.8	No anaesthetic.
6	Mother Fetus	II	23.5 20.0	10.3 8.9	No anaesthetic.
7	Mother Fetus	II	21.7 21.7	10.2 9.3	No anaesthetic.
8	Mother Fetus	II	21.2 22.5	8.9 10.3	Whiffs of chloroform.
9	Mother Fetus	II	28.2 26.5	13.5 12.1	Whiffs of chloroform.
10	Mother Fetus	II	19.5 19.2	8.4 7.9	Whiffs of chloroform.
11	Mother Fetus	II	18.5 18.5	8.4 9.3	Whiffs of chloroform.
12	Mother Fetus	III	26.5 27.5	10.8 11.7	Whiffs of chloroform.
13	Mother Fetus	IV	27.7 27.2	13.1 13.5	Whiffs of chloroform.
14	Mother Fetus	V	29.7 24.2	14.0 13.5	Whiffs of chloroform.
15	Mother Fetus	VIII	27.7 24.7	11.2 9.8	No anaesthetic.
16	Mother Fetus	IX	27.7 27.5	12.6 11.7	Whiffs of chloroform.

pounds, too, are much simpler in structure than protein though, like it, they are characterized by the presence of nitrogen in their molecules.

Besides certain well-known proteins, then, our blood contains a number of other nitrogenous substances. Perhaps, it is fair to regard the blood protein as reserve material and to regard the non-protein compounds as those momentarily engaged in nitrogenous metabolism. The latter, as I have indicated, differ greatly, since they include both nutritive material and waste products; but on account of a certain similarity in chemical behavior they may be estimated collectively, and when grouped in this way are designated as the *non-protein nitrogen* of the blood.

For the estimation of the non-protein nitrogen a remarkably accurate and satisfactory method was devised by Folin. We have employed it in 35 cases in which normal pregnancy concluded with a spontaneous delivery; we found in the case of the mother an average of 25.2 mg. of non-protein nitrogen per 100 cc. of blood and in the case of the fetus 24.9 mg.

The impressive resemblance between

these figures does not depend upon the fact that they represent a mean value. The results are expressed in that form merely as a matter of convenience, for, examined individually, the cases exhibit the same equality of maternal and fetal non-protein nitrogen. Thus, in 20 cases the results for the two organisms did not differ by more than a milligram and in the others the difference was usually less than two milligrams. The most instructive illustration of this similarity in the composition of maternal and fetal blood is afforded by a case of twins in which the mother presented 30 mg. and each infant 30.2 mg. of non-protein nitrogen per 100 cc. of blood.

The equality of the non-protein nitrogen in maternal and fetal blood indicates that its various constituents, belonging in part to the class of foods and in part to the class of waste products, pass freely through the placental partition. Indeed, our findings suggest even more than that. There must be a regulatory mechanism which maintains the same concentration of non-protein nitrogen in the two circulations; and such a strict equality of concentration, we are at a loss to explain on any

other basis than that of simple diffusion. This process, as we know, permits the ready passage of certain substances through a semi-permeable membrane, and to secure an equal concentration on both sides of the partition may be said to be its very aim. However, without further evidence of a more detailed character, it would be hazardous to announce a final conclusion, for each of the substances included in the non-protein nitrogen should be studied separately. As that has been done, we may proceed to examine, individually, the amino acids, urea, ammonia, uric acid and creatinine; for, besides protein, these are the ingredients of the blood, distinguished by the fact that they contain nitrogen.

IV

THE amino acids are crystalline, more or less soluble compounds; and on account of these and other physical and chemical properties they would be expected to be diffusible substances. They actually are, as Abel showed by means of collodion tubes ingeniously contrived to accommodate an artifical circulation of the blood and to arrange for the collection of substances escaping by diffusion through the tube wall. Other experimenters have confirmed Abel's statement that amino acids pass readily across such a permeable partition, and that in general amino acids pass into the body tissues by the process of diffusion.

Until very recently, it was not suspected that amino acids, supplied by the mother, are the material out of which fetal protein is constructed. Albumoses were thought to serve this purpose, for, although they were not demonstrable in either maternal or fetal blood, they were isolated from the placenta itself. These findings were ac-

cepted in support of the view that the placenta is a digestive organ, at first breaking down maternal protein and later assembling the fragments into fetal protein.

AMINO ACID NITROGEN
OF THE PLASMA*

No.	Source	Para	Amino acid nitrogen mg. per 100 cc.	Remarks
1	Mother Fetus	I	5.3 7.0	Remarks.
2	Mother Fetus	II	5.9 7.9	No anaesthesia.
3	Mother Fetus	III	5.3 7.8	No anaesthesia.
4	Mother Fetus	IV	6.5 8.2	No anaesthesia.
5	Mother Fetus	V	7.2 11.9	No anaesthesia.
6	Mother Fetus	I	5.6 7.6	No anaesthesia. Premature infant: 8th month.
7	Mother Fetus	II	6.6 8.3	Whiffs of chloroform.
8	Mother Fetus	II	4.9 6.8	Whiffs of chloroform.
9	Mother Fetus	I	5.0 6.4	Whiffs of chloroform.
10	Mother Fetus	I	5.6 7.3	Morphine and tyramine.
11	Mother Fetus	I	4.5 6.2	Low forceps: Deep chloroform.

*Analyses made by A. H. Morse.

But this hypothesis was never satisfactory and, probably, would not have been announced if, at the time, it had been known that amino acids are abundant in the blood. The proof of this very fundamental fact wrought revolutionary changes in our conception of tissue metabolism and, in particular, left no room for doubt regarding the elementary substances the mother contributes to the new organism for the manufacture of its protein. At present, there is not the slightest excuse for assuming that the placenta synthesizes protein for the fetus. This function the fetal tissues perform for themselves. The requisite amino acids, having been acquired from the mother, are available in the fetal blood. Of this we are sure; but how do they pass through the placental partition? Let us see what light blood analysis throws upon the subject.

It is pertinent that the blood corpuscles are richer in amino acids than the blood-plasma, and also that the corpuscles of the fetus are richer than those of the adult. What part these facts may ultimately play in the detailed explanation of tissue metabolism it is impossible to predict; but I

am doubtful that they have any significance for our immediate problem, since only substances in solution—substances in the plasma—take part in the placental interchange. Furthermore, though many technical intricacies could be enumerated, perhaps, it is sufficient to state that no analytical method at hand includes all of the amino acids in the blood. The method devised by Van Slyke takes into account most of them and this procedure was used in our investigations.

An excess of amino acids amounting to about 2 mg. of nitrogen appears uniformly in favor of the fetal plasma. Even such a small difference in concentration implies that, so far as the amino acids are concerned, some process is added to that of simple diffusion in the regulatory mechanism of the placental interchange. Similar results in connection with the passage of amino acids into various tissues led Van Slyke to give the name "absorption" to the phenomenon in question. This investigator found that if amino acids were injected into the circulation they diffused into the tissues rapidly and an equilibrium was reached when the tissues contained

about ten times as much amino acid nitrogen as the plasma. An equilibrium is reached between maternal and fetal blood when there is only a slight difference of concentration in the two circulations, while the excess of amino acids in fetal plasma indicates that the placenta is capable of absorbing them and also of preventing their departure from the fetus.

V

UNTIL the time of birth, the fetus does not employ the same channels as the adult to get rid of the excretory products formed by the utilization of food. The typical action of the lungs, for example, begins when breathing becomes established in the new-born; previously, the elimination of carbon dioxide has been conducted through the placenta, and this gas, after reaching the mother's circulation, is excreted by her lungs. Similarly, the placenta takes the place of the fetal kidneys. Urea, ammonia, uric acid, creatine and creatinine, the waste products derived from the use of protein by the fetus, are borne back to the placenta, transferred from the fetal to the maternal circulation and finally thrown off in the mother's urine. The mechanism responsible for the transfer of these substances from one circulation to the other, and that alone is of interest here, becomes quite clear in the light of blood analysis, for the results obtained in this way establish the fact that the fetal nitrogenous

waste products pass through the placenta in accord with the principles of diffusion.

Urea, the most abundant of the nitrogenous waste products, is so readily diffusible that its concentration in the blood

URIC ACID

OF THE WHOLE BLOOD*

No.	Source	Para	Uric acid mg. per 100 cc.	Remarks
1	Mother Fetus	I	6.8 5.0	Chloroform.
2	Mother Fetus	I	4.8 4.5	Chloroform.
3	Mother Fetus	I	4.3 4.3	Chloroform.
4	Mother Fetus	I	8.0 8.1	Chloroform.
5	Mother Fetus	I	5.9 5.6	Chloroform.
6	Mother Fetus	II	2.3 2.5	No anaesthesia.
7	Mother Fetus	II	1.8 1.8	Chloroform.
8	Mother Fetus	III	2.2 2.0	No anaesthesia.
9	Mother Fetus	III	3.0 3.3	Chloroform.
10	Mother Fetus	IV	2.0 2.7	Chloroform.
11	Mother Fetus	V	2.2 2.4	No anaesthesia.
12	Mother Fetus	X	2.8 2.2	No anaesthesia.

*Analyses made by L. J. Bogert.

plasma, the corpuscles and the tissues of our bodies is always the same. Consequently, before the facts were actually determined, it would have been a safe prediction that identical quantities of urea would be found per unit volume of the blood of each organism. Our observations verify this prediction, for in a series of 16 normal cases the results gave an average of 10.5 mg. of urea per 100 cc. in the blood of the mother and 10.4 mg. in the fetus. Furthermore, in the presence of a complication, as nephritis, where a relatively large quantity of urea occurs in the maternal blood, a similar value obtains in the fetal blood. The evidence is conclusive, then, that the placenta takes no active part in the elimination of fetal urea, but behaves as a semi-permeable membrane.

"TOTAL" CREATININE

OF THE PLASMA

Author	Mother mg. per 100 cc.	Fetus mg. per 100 cc.	Number of Cases
Hunter and Campbell	1.67	1.75	18
Plass	1.70	1.73	12

As the method we employed to determine the quantity of urea really includes the ammonia which is present in the blood in extremely small amounts, the analytical results just referred to are doubly significant. They make it certain that ammonia, as well as urea, passes through the placenta by diffusion. That the same explanation also holds for uric acid is clear from our figures in the table on page 31; and these are confirmed by the results of Kingsbury and Sedgwick. Finally, the evidence regarding creatinine and creatine which have been studied by Hunter and Campbell and by Plass agrees perfectly with the conclusions just reached. Therefore, we are confident of the passive rôle of the placenta in the transmission of all the nitrogenous fetal waste products. They enter the maternal circulation as freely as if the placenta did not exist, and ordinarily the estimation of the quantity of them in the mother's blood holds valid for the blood of the fetus.

VI

Carbohydrate, the second of the organic foodstuffs to be studied, becomes available for intermediary metabolism in the form of glucose, the blood sugar. An excellent method for its determination devised by Benedict was the one employed in our series of cases. For the mother, the mean value found was 0.132%, and for the fetus 0.115%. Slightly higher values occurred in the maternal blood in 19 of our 24 cases, while the values were identical in both circulations in five cases. Bergsma states that the sugar content of the blood in the two organisms is always the same. However, his work is open to criticism, for the specimen from the mother and that from the infant were not obtained simultaneously; in some instances an interval of twenty minutes elapsed between the times when the specimens were secured.

These facts do not support a hypothesis requiring the action of a placental enzyme. That doctrine advocated by Hofbauer rests chiefly upon his demonstration of fer-

PERCENTAGE OF SUGAR

IN THE WHOLE BLOOD*

No.	Source	Para	Blood-sugar %	Remarks
1	Mother Fetus	I	0.143 0.124	Whiffs of chloroform.
2	Mother Fetus	I	0.097 0.10	Morphine and tyramine.
3	Mother Fetus	I	0.161 0.131	Morphine and tyramine.
4	Mother Fetus	I	0.137 0.141	Whiffs of chloroform.
5	Mother Fetus	I	0.125 0.108	Whiffs of chloroform.
6	Mother Fetus	I	0.155 0.112	Whiffs of chloroform.
7	Mother Fetus	I	0.142 0.106	Whiffs of chloroform.
8	Mother Fetus	I	0.155 0.124	Whiffs of chloroform.
9	Mother Fetus	II	0.126 0.11	No anaesthetic.
10	Mother Fetus	II	0.156 0.124	Whiffs of chloroform.
11	Mother Fetus	II	0.146 0.108	Whiffs of chloroform.
12	Mother Fetus	II	0.115 0.103	Whiffs of chloroform.
13	Mother Fetus	II	0.112 0.086	Whiffs of chloroform.
14	Mother Fetus	II	0.11 0.075	Whiffs of chloroform.
15	Mother Fetus	II	0.125 0.101	Whiffs of chloroform.
16	Mother Fetus	III	0.105 0.096	No anaesthetic.
17	Mother Fetus	III	0.126 0.105	Whiffs of chloroform.
18	Mother Fetus	IV	0.172 0.122	Whiffs of chloroform.
19	Mother Fetus	IV	0.124 0.095	Whiffs of chloroform.
20	Mother Fetus	IV	0.126 0.094	No anaesthetic.
21	Mother Fetus	V	0.132 0.112	Whiffs of chloroform.
22	Mother Fetus	V	0.126 0.13	No anaesthetic.
23	Mother Fetus	VI	0.089 0.06	Whiffs of chloroform.
24	Mother Fetus	VIII	0.185 0.185	Whiffs of chloroform.

*Analyses made by W. H. Morriss.

ments whose function, in all probability, is the preparation of the glycogen, stored in the decidua, for passage to the fetus. The results of blood analysis certainly do not indicate that enzymes are responsible for the transportation of glucose through the placenta, but, on the contrary, speak strongly against it. Thus, in a case of double-ovum twins, where each fetus had its own placenta, the blood sugar of one was 0.099% and of the other 0.096%, while that of the mother was 0.12%. Such findings are inexplicable except on the basis of diffusion, and on this basis higher maternal values promote a steady flow of glucose toward the fetus. In this arrangement to guarantee an adequate supply of carbohydrate to the fetus there is an intimation of its great importance before birth; and when we learn, as we shall, that this inference has the support of facts regarding the fats and lipoids, it becomes even more apparent that the fetus depends to an unusual degree upon the maternal contribution of glucose for the maintenance of its nutrition.

VII

From a long series of observations we obtained analytical data relative to the fats and lipoids which is illustrated by the results in the table. These substances are more abundant in the mother and relatively large maternal values are accompanied by large fetal values; otherwise, the most notable feature of our findings consists in the disparity between the quantities of fats and lipoids in the two circulations. Between the plasmas a similar disparity exists. Here the difference between the maternal and the fetal figures is so great that we may not entertain the possibility of fat passing through the placenta in the way other substances do. Toward explaining such results two alternatives come to mind; either the fats and lipoids cross the placenta with the aid of an enzyme, or they do not cross at all. Although our data would accord with either explanation, leaving the question open, there are at hand observations of a very different kind which decide the matter and teach that the latter interpretation is correct.

FATS AND LIPOIDS*

WHOLE BLOOD

(*mg. per* 100 *cc.*)

No.	Source	Fats	Cholesterol			Lecithin	Remarks.
			Total	Esters	Free		
1	Mother	1120	280	115	165	350	Whiffs of chloroform.
	Fetus	790	170	20	150	260	
2	Mother	885	255	110	145	355	Whiffs of chloroform.
	Fetus	675	160	35	125	250	
3	Mother	940	225	145	80	245	Whiffs of chloroform.
	Fetus	775	125	25	100	175	
PLASMA (*mg. per* 100 *cc.*)							
1	Mother	1240	300	180	120	270	Whiffs of chloroform.
	Fetus	840	180	30	150	200	
2	Mother	945	260	160	100	280	Whiffs of chloroform.
	Fetus	715	170	40	130	200	
3	Mother	960	260	180	80	240	Whiffs of chloroform.
	Fetus	780	95	10	85	115	

*Analyses made by H. J. Stander.

Following the investigations of Hofbauer and of Gage, Mendel and Daniels resorted to vital staining and employed Sudan III, which colors fat red. The animals selected, pregnant rats, were treated by injection of the dye into the maternal circulation. Invariably, as these investigators find, the maternal fat is stained, and not the fetal. Between the tissue affected and that not affected the line of demarcation in the region of the placenta is very sharp. Stained fat cannot be traced in transit through the organ and there is no staining of the fetal fat. Now, these observations, especially in conjunction with the disparity we note between the amount of fat in the blood of the mother and that of the fetus, demonstrate in a convincing way that fat is not included among the materials contributed by the parent to her offspring. The fat of the body of the fetus is manufactured there, almost certainly manufactured from carbohydrate with which the new organism is supplied abundantly. In theory, then, there is no necessity for fats and their derivatives, the lipoids, to pass the placental partition; and the evidence gathered both from biological and

chemical studies substantiates our conclusion that they have no part in the placental interchange.

VIII

Without certain reservations, we may not infer that what we have found true for the placental interchange at full term also pertains to the early months of pregnancy, a period when the thickness and complexity of the walls of the chorionic villi are notably greater than they are later. The simplification of the placental partition occurs at about the 18th to 20th week of pregnancy, and this date marks the beginning of a more rapid rate of fetal growth. During the latter part of pregnancy, at least, the placental partition is passive and behaves like a semi-permeable membrane; the facts at hand, in other words, support *the mechanistic hypothesis* of placental function. Thus, the amino acids, from which fetal protein is built, and glucose, which supplies the requisite energy for tissue construction, pass freely to the new organism in accord with the principles of diffusion. While in the mother's blood, these substances are not more accessible to her own tissues than to the fetus; and probably

the quantity of them which reaches the fetus is regulated by the rate of their consumption in its body.

The interchange of water between the two organisms and of most, if not of all, of the inorganic salts, including calcium, magnesium, sodium, and potassium, takes place in accord with the principles of diffusion. With regard to iron it is impossible, at present, to affirm what arrangements are made for its transportation through the placenta. This intricate and unsolved problem occupies a unique position among the factors of fetal nutrition. Stored in the newly born infant there is a large quantity of iron, so large, indeed, that the quantity is proportionately much greater than in the adult. The purpose of this storage in the newborn, Bunge believes, is to compensate for the inadequate amount of iron in human milk.

The fats and lipoids of the mother's blood, as we have seen, are held in check by the placenta; the fetus manufactures fats out of some other material, most likely out of the glucose contributed by the mother. The manifest difference between maternal and fetal blood in this respect

stimulates our curiosity with regard to the fat metabolism of pregnancy, and this attitude is in harmony with the times, for everywhere at present there is a lively interest in the nutritional rôle of the fats and the lipoids, cholesterol and lecithin. The purpose and fate of the latter, physiologists have not made out satisfactorily, even with regard to animal metabolism in general. But, tempting as speculation is, at the moment we may go no further than the facts; there is a high fat content in the blood of the pregnant woman, a much lower one in the blood of the fetus, and between the two circulations there is no interchange of fats or related substances.

All fetal waste products, including carbon dioxide, which was the first to be thoroughly studied, pass the placenta by diffusion. Active elimination of these substances on the part of the mother's excretory organs maintains their proper concentration in her blood and, simultaneously, there proceeds a steady purification of the blood of the fetus. Less favorable conditions prevail in cases of nephritis and of organic cardiac disease when an unusually large amount of excretory products ap-

pears in the mother's blood, and their concentration in both maternal and fetal circulations is always the same. It is not unlikely, therefore, that in the presence of such maternal complications intra-uterine death may be explained on the basis of an inefficient removal of fetal waste.

IX

In the final analysis, the nutrition of the fetus involves two factors, namely, the peculiar activity of its own organs and the supply of food it receives. The first is the more fascinating, and also the more difficult of study because the isolation of the fetus baffles the most ingenious experimenters. In the absence of specific knowledge regarding the intermediary fetal metabolism our nearest approach to the facts is to accept an analogy with adult nutritional processes. And yet, in doing so, we are conscious of not being logical, for the unusual prominence of certain organs, as the thymus gland, indicates the existence of radical differences between the metabolism of the immature organism and that of the adult.

The second factor in the nutrition of the fetus—its food supply—has been brought within the range of direct observations; and some of the conclusions derived from the study of the origin and the variety of materials incorporated in its body have a

practical application. Thus, there is no diet specifically adapted to the state of pregnancy; the prospective mother may exercise the same freedom as any one else in the selection of food. She should, however, choose what will agree with her and avoid that which she cannot digest and assimilate. Personal experience in the main must guide everyone as to what to eat and most women follow the dictates of appetite after they become pregnant as safely as they did before.

In a practical sense the quantity of the mother's food is more influential than its quality. Popular opinion holds that during pregnancy the mother "should eat for two." This doctrine is erroneous. A diet which has previously been ample will likewise be sufficient throughout pregnancy. And it is not unimportant to emphasize this view, which has the unqualified support of painstaking, scientific investigations, because overeating during pregnancy is much more likely to provoke discomfort than insufficient nourishment. On the other hand, there can be no justification for measures intended to restrict the growth of the fetus, for when rigidly

carried out they tend to weaken the mother. She may be careful, in other words, to avoid overgrowth of the fetus, but should not adopt a diet so limited as to interfere with normal development. So long as her health is properly maintained no thought may be given as to what the size of the fetus is likely to be. At present, provided the physician determines by a thorough, preliminary examination the existence of any disproportion between the size of the fetus and the capacity of the mother's pelvis, he is qualified to decide what the appropriate treatment should be in order to bring pregnancy to a successful termination.

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